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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/386,450	08/31/1999	GERTRUD HOTTEN	P564-9022	1400

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EXAMINER
ROMEO, DAVID S

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/15/2003

29

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/386,450	HOTTEN ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed February 25, 2003 (Paper No. 25) has been entered. Claims 30-41 are pending and being examined.

The terminal disclaimer filed on February 24, 2003 (Paper No. 28) disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of 6,120,760 has been reviewed and is accepted. The terminal disclaimer has been recorded.

New formal matters, objections, and/or rejections:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 30, 31, 35, 36, 41 are rejected under 35 U.S.C. 102(e) as being anticipated by Lee (1, cited by Applicants) in view of Lodish (u29).

This rejection is based upon an effective filing date of January 12, 1993 for Lee.

The present claims are directed to a protein of the TGF-β family encoded by an isolated DNA molecule. Although the protein has the property of being encoded by a DNA molecule, the claims do not indicate the amino acid sequence of the protein. A "coding region" is a sequence in a DNA molecule that encodes the amino acid sequence of all or part of a protein. See Lodish (u29), page G-4, right column, penultimate entry. Accordingly, the claims are directed to or encompass a protein of the TGF-β family comprising all or part of the amino acid sequence encoded by the DNA molecule sequences of the present claims. The present application at page indicates that the start of the "mature" protein begins after nucleotide 1782 [of SEQ ID NO: 1]. Accordingly, the term "mature" encompasses any and all proteins of the TGF-β family beginning anywhere and everywhere after nucleotide 1782 of the present application's SEQ ID NO: 1.

Lee discloses an isolated polynucleotide encoding GDF-5 and isolation and purification of recombinantly expressed GDF-5 (column 4, line 36, through column 7, line 47; Figures 2A-2B; SEQ ID NO: 10). Partial cDNA analysis of a human PCR product revealed no predicted amino acid differences between mouse and human GDF-5 (column 13, lines 23-25). GDF-5 is a member of the TGF-β superfamily of proteins (paragraph bridging columns 2-3). Amino acids 381 to 495 of Lee's GDF-5 are identical to amino acids 387 to 501 of present application's SEQ ID NO: 2, as indicated below:

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ID   US-08-455-559-10     STANDARD;     PRT;   495 AA.
CC    Sequence 10, Application US/08455559
CC    Patent No. 5801014
CC     INFORMATION FOR SEQ ID NO:  10:
CC       SEQUENCE CHARACTERISTICS:
CC         LENGTH:  495 amino acids
CC         TYPE:  amino acid
CC         TOPOLOGY:  linear
CC       MOLECULE TYPE:  protein
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SQ   SEQUENCE   495 AA; 54885 MW; 1212056 CN;

  Query Match           91.0%;  Score 3332;  DB 1;  Length 495;
  Best Local Similarity  91.2%;  Pred. No. 1.50e-278;
  Matches   457;  Conservative   23;  Mismatches  15;  Indels   6;  Gaps   2;

Db      1 MRLPKLLTLLLWHLAWLDLELICTVLGAPDLGQRTPGAKPGLTKAEAKERPPLARNVFRP 60
          |||||||:|||  |||||||:|||||||||||||  |::|||:|||||||||||||||||
Qy      1 MRLPKLLTFLLWYLAWLDLEFICTVLGAPDLGQRPQGTRPGLAKAEAKERPPLARNVFRP 60

Db     61 GGHIYGVGATNA--RAKGSSGQT----QAKKDEPRKMPPRSGGSETKPGPSSQTRQAAAR 114
          |||  ||  |||||  ||||::|||    |:||||||:|:|||:||:| |||  ::|||||:||
Qy     61 GGHSYGGGATNANARAKGGTGQTGGLTQPKKDEPKKLPPRPGGPEPKPGHPPQTRQATAR 120

Db    115 TVTPKGQLPGGKASSKAGSAPSSFLLKKTREPGTPREPKEPFRPPPITPHEYMLSLYRTL 174
          ||||||||||||::|||| |||||||:|||| ||||||||||||||||||||||||||||
Qy    121 TVTPKGQLPGGKAPPKAGSVPSSFLLKKAREPGPPREPKEPFRPPPITPHEYMLSLYRTL 180

Db    175 SDADRKGGNSSVKLEAGLANTITSFIDKGQDDRGPAVRKQRYVFDISALEKDGLLGAELR 234
          |||||||||||||||||||||||||||||||||||| ||||||||||||||||||||||||
Qy    181 SDADRKGGNSSVKLEAGLANTITSFIDKGQDDRGPVVRKQRYVFDISALEKDGLLGAELR 240

Db    235 ILRKKPLDVAKPAVPSSGRVAQLKLSSCPSGRQPAALLDVRSVPGLDGSGWEVFDIWKLF 294
          ||||||  |  |||| |::|| |||||||||||||||:||||||||||||||||||||||
Qy    241 ILRKKPSDTAKPAAPGGGRAAQLKLSSCPSGRQPASLLDVRSVPGLDGSGWEVFDIWKLF 300

Db    295 RNFKNSAQLCLELEAWERGRAVDLRGLGFERTARQVHEKALFLVFGRTKKRDLFFNEIKA 354
          |||||||||||||||||||||||||||||:|:|||||||||||||||||||||||||||||
Qy    301 RNFKNSAQLCLELEAWERGRAVDLRGLGFDRAARQVHEKALFLVFGRTKKRDLFFNEIKA 360

Db    355 RSGQDDKTVYEYLFSQRRKRRAPLANRQGKRPSKNLKARCSRKALHVNFKDMGWDDWIIA 414
          |||||||||||||||||||||||| ||||||||||||||||||||||||||||||||||||
Qy    361 RSGQDDKTVYEYLFSQRRKRRAPLATRQGKRPSKNLKARCSRKALHVNFKDMGWDDWIIA 420

Db    415 PLEYEAFHCEGLCEFPLRSHLEPTNHAVIQTLMNSMDPESTPPTCCVPTRLSPISILFID 474
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Qy    421 PLEYEAFHCEGLCEFPLRSHLEPTNHAVIQTLMNSMDPESTPPTCCVPTRLSPISILFID 480

Db    475 SANNVVYKQYEDMVVESCGCR 495
          |||||||||||||||||||||
Qy    481 SANNVVYKQYEDMVVESCGCR 501.
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Lee also discloses two putative tetrabasic proteolytic processing sites RRKRR and KR-at amino acids 371-375 and amino acids 384-385. Cleavage of the precursor at these sites would generate mature C-terminal fragments of 120 or 110 amino acids in length with predicted molecular weights of 13.6K and 12.5K, respectively (column 4, lines 59-64). The sequence of the mature C-terminal fragment 110 amino acids in length is identical to the corresponding region of the present application's SEQ ID NO: 2, as indicated above.

Accordingly, Lee discloses a protein of the TGF-β family encoded by a DNA molecule comprising the sequences of the present claims, wherein the protein of the TGF-β family is the mature C-terminal fragment 110 amino acids in length that is identical to the corresponding region of the present application's SEQ ID NO: 2.

The proteins of the TGF-β family are initially synthesized as a large precursor protein which subsequently undergoes proteolytic cleavage at a cluster of basic residues approximately

110-140 amino acids from the C-terminus. In each case, the active species appears to be a disulfide-linked dimer of C-terminal fragments. See column 1, lines 38-57. Polynucleotide sequences encoding GDF-5 can be expressed in eukaryotes (column 7, full paragraph 1). Expression of polynucleotide sequences encoding GDF-5 in eukaryotes would result in the formation of a dimer in the absence of evidence to the contrary and because, in each case, the active species of TGF-β family members appears to be a disulfide-linked dimer of C-terminal fragments.

The present claims do not specify which propeptide and signal sequence are intended and for the purposes of this rejection the terms "propeptide" and "signal peptide" are deemed to encompass the "propeptide" and "signal peptide" of Lee's GDF-5.

Claim Rejections - 35 USC § 103

Claims 30, 32-34, 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee (1, cited by Applicants) in view of Lodish (u29) as applied to claim ~~1~~ 30 above and further in view of Oppermann (2, cited by Applicants). ⊗ R 5/14/3

Lee discloses GDF-5, as discussed above. The structural homology between the GDF-5 protein of this invention and the members of the TGF-β family, indicates that GDF-5 is a new member of the family of growth and differentiation factors. Based on the known activities of many of the other members, it can be expected that GDF-5 will also possess biological activities that will make it useful as a diagnostic and therapeutic reagent. See paragraph bridging columns 2-3. GDF-5 contains all of the highly conserved residues present in other family members, including the seven cysteine residues with their characteristic spacing. Among the known family

members, GDF-5 is most highly related to BMP-2 and BMP-4 in the C-terminal portion of the molecule (57% amino acid sequence identity calculated from the first conserved cysteine). See paragraph bridging columns 4-5. The bone morphogenetic proteins (BMPs, osteogenin, OP-1) can induce de novo cartilage and bone formation (column 1, full paragraph 3). Lee is silent with respect to a pharmaceutical composition comprising GDF-5.

Oppermann discloses a bioassay for bone induction that may be used to monitor endochondral bone differentiation activity of a BMP. Bone matrix implants were assayed for bone forming activity. See paragraph bridging columns 57-58. Oppermann discloses a BMP contained on and/or in a natural or synthetically prepared matrix material that can be biologically degraded (column 49, line 20, through column 57, line 35). Oppermann's natural or synthetically prepared matrix material is a pharmaceutically acceptable carrier, diluent or filler, or a dental implant. Oppermann does not teach GDF-5.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make GDF-5, as taught by Lee, and to modify that teaching by making GDF-5 contained on and/or in a natural or synthetically prepared matrix material, as taught by Oppermann, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to determine the bone and/or cartilage inducing activity of GDF-5. The intended uses of the claimed invention and/or pharmaceutical compositions do not result in a structural difference between the present invention and the prior art pharmaceutical compositions and do not patentably distinguish the claimed invention from the prior art. The invention is prima facie obvious over the prior art.

Claim Rejections - 35 USC § 112

Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 is indefinite because it recites the terms "natural" and "synthetically prepared". Because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "natural" and "synthetically prepared" an artisan cannot determine what additional or material limitations are placed upon a claim by the presence of this element. The metes and bounds are not clearly set forth. It is suggested that the claims recite "a matrix".

Conclusion

No claims are allowed.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

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ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
MAY 14, 2003